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Quadrivalent Human Papillomavirus (HPV) Types 6, 11, 16, 18 Vaccine for the Prevention of Genital Warts in Males†

Profile Report

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Human papillomavirus (HPV) infection has a well established association with the development of genital warts and many types of cancer, including cervical, anal, oropharyngeal, and penile cancer.[2,3] It is the most common sexually transmitted infection in the US,[2] with an annual prevalence of 1% of the sexually active population.[3] It has been estimated that 80% of sexually active women will acquire HPV infection by the time they are aged 50 years.[2] Rates among men are also high, with estimates of ≈65–70% of males being infected with HPV.[4] Young people appear to be most at risk, with 74% of annual HPV infections occurring in men and women aged 14–24 years.[2]

While most HPV infections are transient,[2,3] ≈10% lead to persistent infection.[2] Approximately 40 of the >100 known HPV types have been shown to infect the anogenital tract.[2,3] Fifteen of these have been identified as high-risk (including HPV 16 and 18) and twelve as low-risk (including HPV 6 and 11);[2] HPV 6 and 11 are strongly associated with genital warts (>90% association[3]), while HPV 16 and 18 are strongly associated with cervical and anogenital cancers.[2,3] A total of 99.7% of cervical cancers have detectable levels of HPV DNA,[2] and almost 90% of vaginal cancers are associated with HPV.[5] In men, 80–85% of anal cancers[5] and almost 50% of penile cancers[5,6] are associated with HPV infection.

The rate of new cases of anogenital warts is increasing; currently, more than 500 000 new cases occur in the US annually, and a 2003 estimate found that ≈1.4 million people in the US had genital warts.[3] Moreover, results from a recent study have suggested that the incidence and prevalence of genital warts may be becoming higher in men than in women.[7] The societal burden of genital warts, in terms of both cost and loss of quality of life, is significant.[8-10]

The quadrivalent HPV types 6, 11, 16, 18 vaccine (Gardasil®; hereafter referred to as the quadrivalent HPV vaccine) is a noninfectious recombinant vaccine and comprises purified virus-like particles derived from the L1 capsid proteins of HPV types 6, 11, 16, and 18.[11] Each dose contains approximately 20, 40, 40, and 20 μg of each virus-like particle type, respectively, and includes 225 μg of amorphous aluminium hydroxyphosphate sulfate adjuvant (AAHS).[11] It was approved in females in the US in 2006[12] for the prevention of various diseases caused by HPV types 6, 11, 16, and 18, and has recently been approved in males for the prevention of genital warts caused by HPV types 6 and 11.[11] Over 61 million doses of the

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Table I. Features and properties of the quadrivalent human papillomavirus (HPV) types 6, 11, 16, 18 vaccine (Gardasil®)[1]

Featured indication	
Prevention of genital warts (condyloma acuminata) caused by infection with HPV types 6 and 11 in males aged 9–26 y	
Vaccine composition	
Virus-like particles (VLPs) derived from the L1 capsid proteins of HPV types 6, 11, 16, and 18	
Formulated with a proprietary amorphous aluminium hydroxyphosphate sulfate adjuvant (225 μg per dose)	
Dosage and administration	
Route of administration	Intramuscular injection
Dose	0.5 mL (containing 20, 40, 40, and 20 μg of VLPs for HPV types 6, 11, 16, and 18, respectively)
Administration schedule	Three-dose regimen; injections at months 0, 2, and 6
Most common adverse events (≥5% of males aged 9–26 years receiving the quadrivalent HPV vaccine)	
Injection-site pain, injection-site erythema, injection-site swelling, headache, pyrexia	

quadrivalent HPV vaccine have been distributed worldwide.[13] The features and properties of the quadrivalent HPV vaccine are presented in table I.[1]

The quadrivalent vaccine has demonstrated efficacy in the prevention of cervical, vulvar, and vaginal cancer, genital warts, and precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18 in females,[11] and estimates show that, as well as being potentially cost effective,[14] national vaccination programs targeting adolescent females and young women can be expected to result in decreased incidences of HPV infection[15] and genital warts[16] in both females and heterosexual males (HM) as a result of herd immunity.[16] However, no change was predicted for men who have sex with men (MSM; a group with a high prevalence of HPV infection[17]) or females outside the age range for vaccination.[16]

Various arguments exist in favor of nationwide vaccination of males as well as females, including the increased likelihood of herd immunity, increased effect in the MSM population, and decreased incidence of HPV-associated disease in males (potentially more so than is associated with decreased transmission of the virus from females).[12,18] While one analysis indicated that the vaccination of males as well as females may not be cost effective in the US,[19] this study assumed a higher vaccination rate (75% in both sexes) than is currently observed in women in the US and in most other countries,[12] mainly focused on the prevention of cervical cancer (only including other factors [e.g. genital warts, lower vaccination rates] in secondary scenarios),[19] and did not specifically include MSM in any analyses.[19] Other analyses were more positive, one citing substantial public health benefits and cost effectiveness of vaccinating males aged 9–26 years against HPV 6-, 11-, 16-, and 18-related diseases,[20] another finding that vaccinating MSM was a cost-effective method for prevention of HPV-related anal cancer and genital warts.[21] It has been suggested that if vaccination of one sex falls below 75%, both sexes will need to be vaccinated to achieve herd immunity.[18] Nevertheless, debate continues as to the necessity of vaccination in males.

The quadrivalent HPV vaccine is a recombinant vaccine comprising purified virus-like particles derived from the L1 capsid proteins of HPV types 6, 11, 16, and 18.[11]

The vaccine was highly immunogenic in males.[22-25] Geometric mean titers (GMTs) and seroconversion rates for all four HPV types at month 7 in males aged 10–15 years were noninferior to those in females aged 16–23 years,[22] and those in males aged 9–15 years were noninferior to those in females aged 9–15 years.[23] In addition, GMTs and seroconversion rates in males aged 16–26 years receiving the vaccine were higher than in those receiving AAHS control.[25]

Immunogenicity was generally maintained in the longer term (18–37 months), although antibody levels decreased substantially, compared with the levels at month 7.[11,23,25]

Immunogenicity of the quadrivalent HPV vaccine was not affected by coadministration with a diptheria, tetanus, pertussis, and poliomyelitis vaccine (Repevax®),[26] a meningococcal polysaccharide conjugate vaccine (Menactra®) plus a tetanus, diptheria, and pertussis vaccine (Adacel™),[27] or a tetanus, diptheria, and pertussis vaccine (Boostrix™) plus an investigational quadrivalent meningococcal glycoconjugate vaccine[28] in three randomized, open-label trials in mixed-sex populations aged

11–17,[26] 10–17,[27] and 11–18[28] years. Moreover, the immune responses related to the other vaccines being investigated were also noninferior with concomitant versus sequential administration.[26-28] Additionally, neither of the immune responses associated with the quadrivalent HPV vaccine or a hepatitis B vaccine (Recombivax HB®) were affected when the vaccines were coadministered in a population of women aged 16–23 years.[29]

After a median follow-up of 2.9 years, the quadrivalent HPV vaccine was significantly more effective than AAHS control at decreasing the incidence of HPV 6-, 11-, 16-, or 18-related external genital lesions (the primary endpoint) in a randomized, double-blind, placebo-controlled, multicenter study in males aged 16–26 years.[24] The vaccine was 90.4% effective (95% CI 69.2, 98.1) for this endpoint. The most common clinical endpoint was HPV 6- and 11-related condyloma; efficacy was robust against these lesions.[24] No cases of penile/perianal/perineal cancer were reported in either group.[25]

The vaccine is also expected to be protective against genital warts in males aged 9–15 years, as the immune response in males of this age group was noninferior to that in males aged 16–26 years.[25]

Efficacy of the quadrivalent HPV vaccine was also shown with regard to the prevention of persistent and incident HPV infection.[24]

The quadrivalent HPV vaccine was generally well tolerated in males aged 9–26 years.[22-24] The most common adverse events reported were injection-site related,[22-24] and most of these were of mild to moderate severity.[11] Overall, coadministration of the quadrivalent HPV vaccine with other vaccines was generally well tolerated.[26-29]

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A. Giuliano is on the Speaker's Bureau of Merck and Co, Inc., and is a consultant to Merck and Co, Inc.

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